DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

October 6, 1989

Non-voting agency representatives:

Robert J. Frederick, Environmental Protection Agency
Emily M. Gause, Alcohol, Drug Abuse and Mental Health Administration
Bernard Greifer, Department of Commerce
Phillip Harriman, National Science Foundation
Elizabeth A. Milewski, Environmental Protection Agency
Henry I. Miller, Food and Drug Administration
George P. Shibley, Department of Agriculture
Sue Tolin, Department of Agriculture

National Institutes of Health staff:

W. French Anderson, NHLBI
Barbara Byrae, OD
Becky Lawson, OD

Others:

Kay Austin, Environmental Protection Agency
W. Emmett Barkley, Howard Hughes Medical Institute
David Bays, Environmental Protection Agency
Carl Berryman, U.S. Army
Arindam Bose, Pfizer
Michael Broder, Environmental Protection Agency
Charles J. Eby, Hill and Knowlton
Peter Farnham, American Society of Biological Chemists
Jeffrey Fox, American Society for Microbiology
Chris Good, Environmental Protection Agency
Ann Graham, Food and Drug Administration
Jim Hartten, McDermitt, Will, and Emery Law Firm
Carol Lax Hoerner, Stanford University
John E. Jaugstetter, Genentech, Inc.
Dorothy Jessop, Department of Agriculture
Attila Kadar, Food and Drug Administration
Laurie Leach, Animal Health Institute
Stephen Litwin, Veterans Administration
Laura Osgood
John H. Payne, Department of Agriculture
Rex Rhein, Biotechnology Newswatch
Marvin Rogul, University of Maryland
Janet Shoemaker, American Society for Microbiology
Clarence E. Styron, Monsanto Company
Peter A. West, Department of State
John Whalen, National Institute of Occupational Safety and Health
Lisa White, Blue Sheet
Linda Wolfe, Biotechnica International
John R. Wood, Department of Agriculture
Rogers Yocum, Biotechnica International
Larry Zeph, Environmental Protection Agency

I **CALL TO ORDER AND INTRODUCTORY REMARKS**

Dr. McGarrity, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., October 6, 1989. He said the meeting was called pursuant to a **Federal Register** notice which, being 30 or more days prior to today's date, met requirements of the **NIH Guidelines for Research Involving Recombinant DNA Molecules**. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to conclude within one day.

Dr. McGarrity noted that a quorum was present, consisting of 17 members of the Committee, and said every attempt would be made not to limit debate, but to keep the agenda moving, in hopes that all agenda items could be heard and discussed before members had to leave for travel purposes.

Dr. McGarrity noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business. He reminded the committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; ad hoc consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public.

Dr. McGarrity thanked Dr. James B. Wyngaarden, the former Director of the National Institutes of Health, for everything he did for the Committee and for giving the RAC a high priority during his tenure as Director. Dr. McGarrity said he met with Dr. Wyngaarden in his last weeks as Director and had conveyed the Committee's gratitude to him, both orally and in writing, for both his contributions to recombinant DNA activities and his receptivity to advice from the Committee.

Dr. McGarrity noted that Dr. William Raub was the Acting Director of NIH and underlined that RAC was advisory to the Director of NIH. In light of this, persons with minority opinions should voice them so as to provide Dr. Raub with the entire spectrum of opinions on a given topic.

Dr. McGarrity then told the committee that in all voting he would call first for the affirmative, then for the negative, and finally for abstentions. He underlined that if any voting member felt compelled to abstain due to conflict of interest, that such member should notify the Chair so that the record could duly reflect such situations.

Dr. McGarrity then introduced the new Director of the Office of Recombinant DNA Activities, Nelson A. Wivel, M.D. Dr. McGarrity said he had the pleasure of working with Dr. Wivel over the last

few months and formally welcomed him to the Committee. Dr. McGarrity gave a brief synopsis of Dr. Wivel's educational and professional background, noting he had been working at the NIH for the past 24 years, 20 of which were in the Intramural Program of the National Cancer Institute (NCI), doing extensive work on retroviruses and interferons. Before coming to the Office of Recombinant DNA Activities, Dr. Wivel was the AIDS Program Officer in the General Clinical Research Centers Program of the Division of Research Resources.

II. APPROVAL OF THE MINUTES OF THE JANUARY 30, 1989, MEETING (tab 1362)

Dr. McGarrity called on Dr. B. Murray to present the minutes of the January 30, 1989, meeting. Dr. B. Murray said that she read the minutes and found them to be correct in their substance. However, she said in reviewing them her name had been left off the list of participants and felt this was a simple procedural error. She said she had several minor corrections which she would take up with ORDA staff. Dr. McGarrity noted that if typographical errors or non-substantial changes were noted they could be brought to the attention of the staff.

Mr. Carner said that he was pleased with the accuracy of the transcripts, and Mr. McCreery said that he believed the minutes to be most comprehensive.

Dr. McGarrity asked for further comment, and seeing none called for a vote on the motion. The motion to approve the minutes passed by unanimous vote.

III. AMENDMENT TO RECOMBINANT DNA ADVISORY COMMITTEE CHARTER

Dr. McGarrity said it had become apparent through the work of the Human Gene Therapy Subcommittee over the last year that a more orderly and expeditious process was necessary to move items through subcommittees of the RAC for subsequent review by the full committee. He said that it was desirable to have items brought before the various subcommittees and either approved or disapproved within the subcommittee and then brought before the RAC for approval.

Dr. McGarrity said the change to the Charter came about from initial wording by Dr. Wyngaarden which had been discussed by the RAC at its January 30, 1989, meeting and modified slightly. He reported the Charter had been changed and the following wording incorporated:

> "All proposals referred to a subcommittee for formal review must be approved or disapproved by a majority of a quorum of the subcommittee members before being submitted to the parent committee. If the proposal is deferred by a subcommittee for

two successive meetings, the investigator may appeal this decision by application to the full committee."

Dr. McGarrity said this would produce a more orderly progression of events from subcommittee to final committee action.

IV. **PRESENTATION FROM THE NATIONAL RESEARCH COUNCIL'S STUDY ENTITLED: "FIELD TESTING GENETICALLY MODIFIED MICROORGANISMS: FRAMEWORK FOR DECISIONS"** (tab 1361/I, 1369, and 1373)

Dr. McGarrity said in 1980-81, the RAC wrestled with the problem of reviewing certain experiments, namely those involved with drug resistance, antibiotic resistance, human gene therapy, toxins and environmental release. Prior to that time such experiments were not permitted. However, it became apparent that use of recombinant DNA in an agricultural setting would be of great importance. Since any such research would eventually have to be performed in the open outside the laboratory, the RAC set up the Subcommittee on Environmental Release to study the question. The Subcommittee on Environmental Release was chaired by Dr. McGarrity and developed a document entitled **Points to Consider on Environmental Release of Microorganisms and Plants That Contain Recombinant DNA.** This document was eventually split into two documents, one for microorganisms and one for plants, and eventually one was developed for animals as well.

Dr. McGarrity said it became apparent the NIH was not the place to review proposals for environmental release and both the U.S. Department of Agriculture (USDA) and the Environmental Protection Agency (EPA), as well as some other Federal agencies, should become the focal points for review of such proposals. The National Research Council (NRC) was empowered to perform a study of environmental release and the report (tab 1369) and an executive summary of the report (tab 1373) are the results of this study. Dr. Wivel noted that copies of the NRC monograph were distributed to members of the RAC at the table. Dr. McGarrity called on Dr. Clifford Gabriel of the NRC to brief the Committee on the report.

Dr. Gabriel said the process began in 1984, when Dr. John Burris (now Executive Director of NRC) was hired to study environmental release. However, due to uncertainty as to the various roles to be played by many agencies within the Federal Government, the proposal was never funded.

In 1987, the National Academy of Sciences commissioned Art Kelman to lead an effort which produced a "White Paper" on the topic which proved to be a catalyst for funding the project resulting in the current study. It was determined that plants and microorganisms would be the most useful to study and funding for this project was granted in October of 1988.

A steering committee was chosen and subcommittees on plants and microorganisms were set up. Many experts, including Drs. Anne Vidaver, James Tiedje, Richard Lenski and Richard Mack, were called upon and functioned as a committee of scientists. Dr. Gabriel noted that some criticism over conflict of interest and bias has come forth, but that he felt the Academy process worked extremely well, resulting in appropriate conclusions.

Dr. Gabriel said the steering committee wanted to establish a data base, based on past experience applicable to field testing genetically modified plants and microorganisms, as a point of departure in determining what regulators would need to address in assessing risk. It was felt that enough information was available to make reasonable predictions on the relative safety of such experiments.

The three components of the framework of the report are: (1) familiarity, (2) confinement or control, and (3) potential effects on the environment.

The concept of "familiarity" was deemed to be the past experience gleaned through classical techniques such as embryo rescue and hybridization, and using these results to help predict whether an introduction will be safe and what it will do in the environment.

"Confinement or control" could be viewed via knowledge of plant biology, how plants out-cross and how they escape confinement. It was felt current that procedures were adequate to be able to review proposals and to set confinement so as to ensure no harm to the environment. However, for microorganisms, the committee felt that issues of control and effects were not certain enough regarding genetic exchange and spread. Because of this, an indicator would be used which would be based on "level of uncertainty."

Potential effects on the environment then could be ascertained by taking the familiarity and confinement/control issues and then considering the level of uncertainty in arriving at an index of potential effect.

Dr. McGarrity asked how many people were on the actual working committee. Dr. Gabriel said the steering committee consisted of nine individuals and between six and ten on the subcommittees.

Dr. Riley said she believed this was a valuable report in that it emphasized the hazard more than the process, thereby excluding consideration of the technique used in constructing the organism in question. This should be a useful reference for many years.

Dr. Gabriel said the report notes gaps in the current Coordinated Framework when it comes to regulating organisms. One example is the use of microprojectiles to transform plants, without use of

pathogenic DNA sequences. The Coordinated Framework should take such experiments into account, not because the technique creates or presents a greater level of risk, but because such plants should be looked at in light of potential hazard, regardless of technique employed.

Dr. Atlas said he reviewed this matter for the Academy and EPA. The scientific community has found the word "familiarity" a peculiar one to use in that one can be "familiar" with something and know that it possesses high risk and danger to the environment. Yet the document tends to leave one with the impression that if something is "familiar," it is qualified for release. However, the document clearly presents a risk-based orientation for decisions about whether or not to release. Thus, drawing upon the existing data base and state of knowledge of the specific organism and the environment into which it is to be released, rather than the process of how the organism was created or, necessarily, the purpose of its release.

Dr. Atlas said he did not know whether this document would form a basis for EPA regulation. He expressed concern that EPA make sure that any regulatory changes it effects are properly coordinated with the RAC and the NIH to ensure there are no conflicts between what EPA rules as a safe experiment and what the RAC or NIH perceives as safe. Of equal concern, is the definition of "Recombinant DNA," which may cause problems if different Federal agencies use different definitions for the same word. He stated that the view of the RAC is currently much narrower on what requires review in comparison to the NRC report.

Dr. McGarrity said Dr. Atlas' point was interesting because the NIH Guidelines were amended to indicate that if a proposal were to come before the RAC, but was being reviewed by a regulatory agency, that the RAC would defer to that agency. He said it was conceivable that the EPA could exempt a proposal and then the same proposal could be referred to the RAC to examine. He asked staff to look into such a scenario.

Dr. Vidaver said the same questions should be asked as regards to RAC interface with USDA, which is still a somewhat cloudy issue. In reference to the term "familiarity," she said the committee had struggled very hard to find another term but she felt in reading the report that its concept and definition was made clear.

Dr. McGarrity thanked Dr. Gabriel for his presentation to the RAC and said he and all the members of the RAC were looking forward to reading the full report. He said he was surprised to hear from Dr. Vidaver and Dr. Nina Federoff, in a report to the RAC at a previous meeting, that at least 100,000 releases of micro-organisms and pathogens had been released into the environment with no untoward results. He said it was reassuring to have a

scientific basis for allaying concerns in this area.

V. **AMENDMENT OF SECTION I-B OF THE NIH GUIDELINES** (tab 1361/I, 1364 and 1365)

Dr. McGarrity called on Dr. Riley to lead off discussion of this topic. Dr. Riley said the Subcommittee on Revision of the **NIH Guidelines** had met and, rather than bringing firm recommendations forward, had decided to put forward various alternatives on several aspects of the definition of "recombinant DNA" for discussion by the full Committee.

Dr. Riley said the Subcommittee had posed the following question:

> "Are there any new biohazards to be expected from introducing the new techniques for getting DNA into a cell?"

Dr. Riley said, the conclusion drawn by the NRC after long study, that the process of making a recombinant organism has no direct bearing on the degree of hazard of the resultant product, but that knowledge of the recombinant product is what is important in determining whether or not an experiment should be supervised or monitored in some way, points to a negative answer to the question posed.

Dr. Riley said the Subcommittee did make a suggestion for a change in the definition of "recombinant DNA," as it appears in Section I-B of the **NIH Guidelines.** The following phrase would be inserted:

> "molecules which are constructed inside living cells by joining enriched segments or their synthetic equivalents of DNA to cellular DNA...."

This would cause Section I-B to read:

> "In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments that can replicate in a living cell, (ii) **molecules which are constructed inside living cells by joining enriched segments or their synthetic equivalents of DNA to cellular DNA,** or (iii) DNA molecules that result from the replication of those described in (i) and (ii) above."

Dr. Riley said the majority of the committee felt the new technology of polymerase chain reaction (PCR) amplification was not covered in the existing definition because utilizing PCR enrichment did not require use of a vector DNA. Further, a donor gene could be introduced with no covalent bond simply by PCR

enrichment of the donor sequence. Yet another view was that enrichment was not even required, that non-enriched bulk DNA could be introduced into recipient cells producing a multitude of genetically heterogeneous progeny which could be examined and scored for specific traits of interest.

Dr. Riley said this produced one alternative, whether the language should be confined to "enriched segments of DNA," or whether it should be widened to include "any DNA being introduced," and omit the "enriched" terminology.

Dr. Riley said another alternative would be to include the word "foreign" in the phrase to clarify it, i.e., "molecules which are constructed inside living cells by joining enriched segments or synthetic equivalents of foreign DNA to cellular DNA." She said this would exempt all self-DNA recombination experiments and obviate the need in other sections of the **NIH Guidelines** to immediately define large categories of exemptions for introduction of like DNAs.

Dr. Riley said the Subcommittee also felt new techniques for introduction of DNA should not be described in the section on definition of recombinant DNA; however, they felt there should be a form of addressing these in procedural portions of the **NIH Guidelines**.

Dr. Riley summarized the alternatives which she had explained and asked for discussion on these alternatives.

Dr. Vidaver said the Subcommittee had made an excellent analysis of the issues and said she didn't think the new technologies could be ignored, but rather discussed in proper places in the **NIH Guidelines**. She said the concept of "foreign" DNA could be dealt with in other portions of the **NIH Guidelines**, and the phrase "enriched segments of DNA" could be misinterpreted. She said the value of the NRC report was that it was product-oriented, not process oriented. If this were followed to its logical conclusion, a case could be made for doing away with the **NIH Guidelines** entirely. However, she said the Committee should be cognizant of concerns in the scientific community that new techniques not fall through cracks and suggested that the RAC could perhaps simply send an advisory letter to the Institutional Biosafety Committees (IBCs) on the subject and not modify the **NIH Guidelines**.

Dr. Vidaver said such letters could generally state that, "IBCs should consider receiving notification of general protocols for experiments that involve newer genetic modification techniques, besides those involving recombinant DNA." She said this would alert IBCs to assess the adequacy of safety conditions proposed for experiments which may be potentially hazardous such as experiments involving potent vertebrate toxins.

Dr. Vidaver said such an advisory letter would show that the RAC was not restricting its purview to recombinant DNA but that it recognized the newer techniques to be neither more or less hazardous than others. The RAC is concerned about the degree of hazard and biosafety to both the investigator as well as the environment.

Dr. Bourquin said the Subcommittee had extensive discussion on product versus process and had considered RAC to have considerations in both areas. He said the RAC must first describe the process for which it has jurisdiction. Then the product, or degree of hazard, becomes a concern.

Dr. Clewell said the use of the word "enrichment" in the definition should be taken to encompass not only PCR enrichment but chromosome isolation and fragmentation as well.

Dr. Neiman said one difficulty in making changes such as these is the ramifications of those changes on other portions of the **NIH Guidelines**. He cited the example of ordinary transformation experiments in bacteria. If one transformed with "enriched DNA," would the exceptions listed in the latter parts of the **NIH Guidelines** still hold true for such experiments or cause unintentional regulation of such experiments?

Dr. Riley said the Subcommittee had intended that any like-DNA experiments would be exempted immediately from the **NIH Guidelines**. She said the Subcommittee expected that monitoring provisions of the **NIH Guidelines** would apply only where a degree of hazard could be expected and known non-hazardous experiments would be exempted.

Dr. Neiman said all the unintended regulatory implications appear to have been dealt with, although before voting for such a proposal he requested reassurance on that point. Dr. Riley agreed this was a reasonable position to take.

Dr. Atlas said he had a similar feeling. He preferred to leave the word "foreign" out of the definition, feeling that it was covered in exemptions later on. Further, he felt specification of PCR was improper because this resulted in a definition which was process oriented. He said if the amplification aspects were kept broad with reliance on later exemptions in the **NIH Guidelines**, he would feel comfortable with it.

Dr. R. Murray said he thought the purpose of redefining "recombinant DNA" was to close loopholes. He felt this was still not a broad enough definition, and he was unclear of the intent of the new definition.

Dr. Schaechter said his view was that the intent was to cover procedures which did not legally fall under the term "recombinant DNA" but which would achieve the same end, this would prevent people from being able to use terminology to circumvent application of the **NIH Guidelines** to an experiment.

Dr. R. Murray said Dr. Vidaver's comments in which she implied the possibility of doing away with the whole process and picking out only specifically dangerous areas, was what prompted his remarks. He said he considered a legal evaluation of the significance of these changes to the rest of the document as being critical before a formal vote could be taken. He asked Dr. Vidaver if she was serious about abolishing the RAC, since this was considered at one point when it was shown that the vast majority of experiments were not harmful. Dr. Vidaver said she had just raised the issue for discussion. A scientific case could be made to abolish the RAC, but she didn't believe it was politically feasible or practical.

Dr. Riley said it had come to her attention that IBCs at some universities were treating amplified DNA as if it were recombinant. In a sense, expansion of the definition would not be creating a new definition, but merely following the practice currently in place.

Mr. Mannix said he felt another way to cover the "moral equivalent of recombinant DNA" was to add a sentence to Section I-A, the purpose of the **NIH Guidelines**, to say, "The intent is to cover recombinant DNA molecules, organisms containing the same and DNA and organisms containing the same produced by similar techniques." Then IBCs can determine what the "moral equivalent of recombinant DNA" is and act accordingly. He said he felt a change in the definition would raise too many complications.

Dr. McGarrity said this suggestion had been raised in the Subcommittee. As many as three years ago, a lawyer on the Subcommittee had advised that it was better to change something else within the **NIH Guidelines**, either by footnoting or explanation in other sections, rather than to change an existing definition. For this reason, a change in definition was not recommended at that time.

Dr. Erickson said he did not know how investigators would know to go to the IBC with a new experiment. Perhaps the publicity surrounding a change in definition would prompt investigators to seek review of new experiments in PCR and chromosomal segmentation, which may go unreviewed unless a definitional change is made.

Dr. Atlas said a change in definition was clearly needed. He cited the case of his own IBC which had expanded its own definition of recombinant DNA to include PCR-amplified DNA, even

when not transferred. Clarification is necessary to restrict IBCs in many cases to what should be deemed recombinant DNA, that is actual transfer and recombination events.

Dr. B. Murray said, from an investigator's point of view, it is easier to simply look in the definitions than to search through the entire document reading all the footnotes in order to determine if an experiment is covered or exempt.

Dr. Roberts said part of the intent of using the word "enriched" was to exclude natural transformation processes, bacterial transformation, or simply isolated DNA. From what has been said, PCR alone is the basis for any change being made. Perhaps the word "synthetic" describes this without using the word "enriched," which seems to confuse the issue. Using "synthetic" would include PCR experiments. He asked that the focus be placed on the new technology which would produce something that, at least, is as novel as the original recombinant DNA.

Dr. Erickson said a wider definition was useful because it allowed for doing such things as chromosomal segmentation and insertion to produce a transgenic animal which should be covered under the **NIH Guidelines**. He cited this as an example of an enrichment experiment that did not include polymerase chain reaction technology.

Dr. Roberts said he wanted to be more conservative and keep the focus of the new definition as narrow as possible so as not to pull in semi-natural processes.

Dr. Gellert said he supported a broader definition of "enriched segments" because as new techniques of enrichment are developed, a narrow definition will result in the RAC having to re-examine this issue every two or three years. It would be better to stick with a broad definition and have exemptions elsewhere in the **NIH Guidelines**.

Dr. Neiman asked for two clarifications. He said that the Human Gene Therapy Subcommittee discussions centered around the probability that people could create bulk DNA from a microorganism or virus and that could be used for creating transgenic animals. He said he was unclear if, by exempting bulk DNA from the definition of recombinant DNA, whether viruses were included or excluded in that. Secondly, he asked whether biochemically amplified or naturally amplified viral DNAs were sufficiently heterogeneous that legitimate investigators would not use them for transgenic experiments and seek approval through ordinary peer review processes rather than going through an IBC. He asked whether this discussion referred to transformation with complex organism DNA. Dr. Riley replied that this was the intention of the language.

Dr. Schaechter said a barrier had been crossed when taking these experiments from the test tube to the cell because natural processes take place constantly within a cell and one cannot exclude biology from exemptions, but the words "amplified" and "enriched" have taken care of the normal ordinary processes.

Dr. Schaechter added that "foreign" is not defined in a precise way in biology. In different biological systems, its definition shifts. However, leaving out the word "foreign" poses some danger in that the definition can be trivialized if all natural processes are viewed as exempt. He asked for further discussion on this issue.

Dr. Henry Miller of the Food & Drug Administration (FDA) suggested that Mr. Mannix and Drs. Vidaver and R. Murray had come up with the most adequate solution and that is to revise the whole approach to a product-oriented approach and get away from process altogether. He noted the NRC report pointed out the uselessness of a process-based approach to oversight and that the RAC has been a prototypical case in point. At present, some pathogens that are of genuine concern are exempt and yet some organisms of trivial concern require review.

Dr. Miller said he thought it was "really time to serve the NIH and the research community better by considering making the **NIH Guidelines** voluntary and really phasing them out or placing them in a position of much lower impact." He said the current "pretended viability" of the recombinant DNA approach is to send a message abroad to organizations such as the European Economic Community and others that a process-based approach to oversight or genuine regulation on genetic engineering and its products is viable, while our own National Academy of Sciences has twice come to the conclusion that it is not.

Dr. McGarrity said Dr. Riley had underlined in her comments that the definition should not be process-oriented. New techniques of introducing DNA should not be described in the definition. He added that Dr. Roberts also made similar points, although it was mentioned that when looking at product one cannot ignore process totally. Dr. McGarrity asked Dr. Miller what led him to believe that the Subcommittee or the RAC was saying the definition should be process-oriented.

Dr. Miller replied that this definition would exempt, at the outset, a lot of old techniques which can yield products that are of equal or more concern and which generally render products that are less precisely characterized and more unpredictable than PCR and some of the other newer techniques. This approach produces a dichotomy in logic.

Dr. Riley said the subject had been discussed many times, but the RAC was created to deal with potential hazards of recombinant

a future meeting.

At this point, Dr. McGarrity called a recess. Dr. McGarrity reconvened the Committee and noted several members of the RAC were completing their terms as of this meeting. He presented certificates acknowledging service to the RAC to Dr. Paul Neiman, Dr. Jeffrey Roberts, and Mr. Robert McCreery and thanked them for their efforts, adding that over the past four years he believed much had been accomplished for which these members should be proud. He also said certificates would be mailed to those members who were not in attendance but who were completing their terms, namely Drs. Joseph Pagano, Gerald Musgrave, and Charles Epstein.

Returning to the issue at hand, Dr. McGarrity asked Dr. Riley if she had a motion to present. She moved that "the RAC publish in the **Federal Register** that the RAC is considering making a change in the definition of *recombinant DNA*," and then publish the proposed text and that public comment is being sought before action will be taken. She said the text should read:

> "In the context of these Guidelines, recombinant DNA molecules are defined as either: (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (ii) molecules which are constructed inside living cells by joining enriched segments of DNA or their synthetic equivalents to cellular DNA; or (iii) DNA molecules that result from the replication of those described in (i) and (ii) above."

Dr. Schaechter asked if "cellular DNA" included plasmids and episomes, or whether "intracellular DNA" would be a better term. Dr. McGarrity said he believed it was not necessary to change the term. However, since plasmids are intracellular Dr. Riley accepted this change. Dr. Erickson seconded the motion and offered a friendly amendment to include mentioning the regional meetings in the motion. Dr. Riley said she believed it better to make that in the form of a second motion. Dr. Erickson agreed and seconded the motion as made by Dr. Riley.

Mr. Mannix offered an amendment that the notice be phrased so as to be clear that the RAC is open to alternatives not involving a change in definition, such as a change in the scope of Section I-A of the **NIH Guidelines**, which would achieve the same end. Dr. Riley said that would complicate the issue and bring about conflicts between how RAC is defined and how recombinant DNA is defined.

Mr. Mannix said if this were a rulemaking process, it would equate to the difference between a specific Notice of Proposed Rulemaking and an Advance Notice. He said the Advance Notice is

a bit more tentative and open to alternatives and would let the public know that the Committee might have to make further revisions or more specific proposals before acting. He said he did not think there was consensus on the particular language on which the RAC was prepared to act quickly.

Dr. Riley said the intention of her motion was that the RAC was publishing this as a possible change and seeking comment on it, not that it was a change that was being adopted by the RAC. She asked if Mr. Mannix could offer clarifying wording to ensure this point was being made.

Dr. McGarrity said this could be accomplished in the form of introductory language included for publication in the **Federal Register**. He said there would still be leeway to use alternate language or introduce other concepts. This would not mean this wording is the only wording that could be voted on. Dr. Atlas said he felt this would result in a finally worded motion put forth by the Subcommittee which would require another period of comment before coming back to the RAC.

Dr. Neiman suggested preceding the wording of the motion with a sentence to the effect that, "advances in molecular genetics have come to the attention of the RAC and for which reason it is considering the following change." Dr. Riley said this would be acceptable.

Dr. Shibley asked if Dr. Vidaver's alternative suggestion should not be considered. Dr. McGarrity asked for clarification as to her suggestion. Dr. Vidaver said she suggested an advisory notice be sent to IBCs as a mechanism to take care of some of the questions and concerns expressed in the letter from the National Wildlife Foundation. Dr. McGarrity said he understood this to be a stop-gap measure while seeking a more global solution. Dr. Vidaver replied it could be viewed that way or used as an alternative, if the perception was that the current **NIH Guidelines** were essentially process based.

Dr. McGarrity said he believed this to be yet another issue for discussion unrelated to the motion on the floor. Dr. McGarrity asked Dr. Wivel to restate the motion on the floor. Dr. Wivel restated Dr. Riley's wording:

> "In the context of these Guidelines, recombinant DNA molecules are defined as either: (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (ii) molecules which are constructed inside living cells by joining enriched segments of DNA or their synthetic equivalents to intracellular DNA; or (iii) DNA molecules that result from the replication of those described in (i) and (ii) above."

Dr. McGarrity called for a vote on the motion. The motion carried by a vote of 15 in favor, 1 opposed, and no abstentions.

Dr. McGarrity called on Dr. Erickson. Dr. Erickson made a motion that, "hearings be held at two or more sites in the country to elicit comments on this proposed change." Dr. Gellert seconded the motion.

Dr. McGarrity asked if the purpose of these meetings was to be more global discussion of RAC and recombinant DNA activities or whether it was meant to be only for discussion of the proposed change to the **NIH Guidelines**. Dr. Erickson said he felt such meetings would elicit a full response to many RAC activities. This may be beyond the scope of the **NIH Guidelines** and a narrower focus on the change in definition will allow the RAC to accomplish its goal.

Dr. Neiman supported the motion and said this proposal would change the RAC from being "the gene splicing committee" to the "new stuff committee." Its responsibility will extend to changes in molecular genetics that may be perceived by the public to raise the same sorts of concerns that recombinant DNA did originally. He said a discussion of this by the community would result in the RAC knowing whether it is an important structure that should be developed or whether it is, as Dr. Miller indicated, an artifact of the past.

Dr. R. Murray asked Dr. Erickson to accept a friendly amendment to change the wording of his motion to add the phrase "and its implications for the RAC," to the end of the motion, which would make it clearer that broader implications are being considered. Dr. Erickson agreed to amend the motion to read that, "hearings be held at two or more sites in the country to elicit comments on this proposed change and its implications for the RAC."

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion carried by a vote of 15 in favor, none opposed, and 1 abstention.

Dr. Atlas asked who was going to hold the hearings. Dr. McGarrity replied it would be best for staff to organize but that perhaps one meeting at NIH and two meetings at other locations would be apropos.

Dr. R. Murray asked if the RAC had held such meetings before. Dr. McGarrity said he didn't think the RAC had done so. The NIH had previously done so on issues such as animal welfare and human subjects of research, as well as regional meetings of the Director's Advisory Committee focused on the grant review process. Dr. R. Murray asked that these meetings be open to all

members of the RAC, not only members of the Subcommittee, in an effort to elicit better response and representation at these meetings.

Dr. Schaechter suggested holding one such meeting in conjunction with a meeting of the RAC, perhaps the day before. Dr. McGarrity said it might be a good idea but cautioned that **Federal Register** notification procedures would still come into play and asked Dr. Wivel to have staff work out the details.

Dr. Schaechter said he found merit in Dr. Vidaver's suggestion of an advisory to IBCs and asked if it warranted further discussion. Dr. McGarrity said he would leave that up to the Committee. Dr. McGarrity said he sensed Dr. Vidaver felt she would like to hear comments from the community first, and she agreed.

Dr. Sue Tolin of the USDA said an active mechanism to seek IBC participation in the regional hearings would be advisable. In that way, ORDA and the RAC could gain first-hand knowledge of the thinking in the field.

There being no further discussion on this topic, Dr. McGarrity welcomed Dr. LeRoy Walters of the Kennedy Institute of Ethics back to the Committee and asked him to lead the discussion of agenda item VI, **Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into Human Subjects.**

VI. **"POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF PROTOCOLS FOR THE TRANSFER OF RECOMBINANT DNA INTO HUMAN SUBJECTS"** (tabs 1361/II, 1366 and 1367)

Dr. Walters thanked Dr. Childress and his special subcommittee which met on March 31, 1989, to provide recommendations to the Human Gene Therapy Subcommittee, which met on July 31, 1989. He said he would highlight the five major changes to the **Points to Consider** which were recommended by this special subcommittee:

1. The title of the document is changed to **Points to Consider for Protocols for the Transfer of Recombinant DNA into Human Subjects.** He said this would conform to practice, encompassing both diagnostic and therapeutic studies.

2. The proper name of the Subcommittee has been inserted, to reflect the change from the prior working group terminology throughout the document. He said the Subcommittee stopped short of changing the name of the Subcommittee to the "Human Gene Transfer Subcommittee," in part because it would require a change in the Charter of the RAC, which is a lengthy process.

3. Investigators may now indicate which points are irrelevant to their applications, rather than feeling obliged to respond to all 107 questions. Further, if a proposal is only slightly modified, the investigator may refer back to the previous proposal.

4. Addition of non-therapeutic human gene transfer protocols which would include diagnostic studies such as the Anderson-Blaese-Rosenberg TIL experiment which the RAC has approved.

5. A change in terminology from "possible adverse effects of gene therapy" to "possible adverse effects of the experiment," thus reflecting the larger purview of the RAC and the Human Gene Therapy Subcommittee in considering non-therapeutic human gene transfer experiments

Dr. Walters said the Human Gene Therapy Subcommittee accepted virtually all of the recommendations of the special subcommittee and proposed some additional changes to the **Points to Consider**, including dealing with some controversial issues.

The question of germ line alterations was discussed at length. The current wording of the first sentence of paragraph 7 of the **Points to Consider** is:

> "The RAC and its Subcommittee will not, at present, entertain proposals for germ line alterations, but will consider for approval protocols involving somatic cell gene therapy."

The subcommittee felt the use of the word "entertain" should be changed to "approve." The Subcommittee wants to make it clear to the scientific community that it does not, out of hand, intend to disregard proposals for germ line alterations if an investigator has a good reason for proposing such an experiment and that it wished to see such proposals. However, after considerable discussion, the Subcommittee left the wording intact.

Further, Dr. Walters said the Subcommittee discussed whether the scope of the definition of "germ line alterations," as defined in the final sentence of paragraph 7, should be broadened. However, they ultimately made no changes in its definition to allow for a narrow definition of "germ line alteration" which would allow maximum space for somatic cell gene therapy or gene transfer.

Dr. Walters said the Subcommittee added the following detail to point 2-b, "Laboratory studies of gene transfer and expression:"

(1) What animal and cell culture models were used in

laboratory studies to assess the in vivo and in vitro efficacy of the gene transfer system? In what ways are these models similar to and different from the proposed human treatment?

(2) What is the minimal level of gene transfer and/or expression that is estimated to be necessary for the gene transfer protocol to be successful in humans? How was this level determined?

(3) Explain in detail all results from animal and cell culture model experiments which assess the effectiveness of the delivery system (part 2.a. above) in achieving the minimally required level of gene transfer and expression (2.b.(2) above).

Dr. Walters said the Subcommittee added the following to point 4, "Public health considerations:"

e. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to the patient? Are such concerns applicable to health care personnel?

And finally, Dr. Walters said, the Subcommittee added the following to point 5-b, "Qualifications of investigators, adequacy of laboratory and clinical facilities:"

Will the research institution designate an ombudsman, patient care representative, or other individual to help protect the rights and welfare of the patient?

Dr. Walters said the document was the result of a two-step process, and that he was bringing it before the RAC for its consideration.

Dr. Childress thanked Dr. Walters for his excellent summary. He reminded the RAC of the requirement for an annual review of the **Points to Consider**, which had also been altered in this new version to say a review will be carried out "periodically, as needed." He reiterated Dr. Walters' suggestions that the Anderson-Blaese-Rosenberg proposal had shown the document needed to be open to innovation in technology and the process of reviewing that proposal had been very useful in developing this new document. He added there were many small changes in verbiage, but they had no major impact on the overall document. Dr. Childress thanked everyone who had worked on this. He believed this new document would be more useful to the Subcommittee, the RAC, and investigators in the field.

4997B - "Viruses or viroids for human veterinary, plant or laboratory use except hog cholera and attenuated or inactivated systems."

4998B - "Bacteria, fungi and protozoa, except those listed in Supplement No. 1 to Part 799.2, Interpretation 28."

Mr. Seevaratnam added that prior to February 23, 1989, an individual validated license (IVL) was required by the Department of Commerce for export of all etiologic agents to all destinations except Canada. However, on February 23, 1989, the Department of Commerce issued an interim rule which changed the status of control not only for items controlled for national security reasons unilaterally but for etiologic agents as well.

The proposed rule, as published in the **Federal Register** of February 28, 1989, released all Class 1 agents and certain Class 2 agents based on level of pathogenicity. However, it retained controls on the Residual Class 2, all of Class 3 and Class 4 agents based on pathogenicity. This rule was proposed after agreement of several agencies that certain etiologic agents should be controlled under the umbrella of "foreign policy," with the objective of concern over their potential for biological warfare. Further, it retained controls on all genetically manipulated agents, regardless of their class.

The last classification, all genetically manipulated agents, brought about a protest from the public and the scientific community. This was expected, but because of the lack of time available to formulate a new policy and lack of expertise, it was impossible for the Department of Commerce to do otherwise. But, since it was a "proposed" rule, the Department of Commerce sought advice and technical input from the scientific community in order to narrow it to a more meaningful control.

Mr. Seevaratnam said the Department of Commerce had 10 technical advisory committees, one of which is the Biotechnology Technical Advisory Committee (BIOTAC) whose duties are:

> "The BIOTAC advises and assists the Department of Commerce and other appropriate U.S. Government agencies with respect to questions involving technical matters, worldwide availability and actual utilization of production technology licensing procedures which affect the level of export controls applicable to goods and technology under its purview."

Mr. Seevaratnam said the BIOTAC had reviewed the proposed rule as it related to controls on genetically manipulated agents, and they recommended that it be revised as follows:

> "Those genetically modified organisms that contain coding DNA sequences associated with pathogenicity arising from controlled source organisms remain under export control."

He said what this did was narrow the controls from "all genetically manipulated organisms" to only those containing certain DNA coding sequences of concern.

This recommendation was then reviewed by a technical task group and an interagency working group who both have agreed with it. It is expected to be issued formally no later than the end of this year.

Mr. Seevaratnam said the term "genetically modified organism" has been defined as:

> "An organism to which genetic material has been added or deleted, either via recombinant DNA techniques or by other means."

Mr. Seevaratnam said the Department of Commerce is seeking the expertise of the scientific community to determine if this definition needs to streamlined or if it is even necessary. He noted that to change the definition would require interagency agreement from the Department of Defense and the Department of State and asked anyone concerned to write to the following:

> William L. Clements, Director
> Office of Technology and Policy Analysis
> U.S. Department of Commerce, Room 4069
> Washington, D.C. 20230

Mr. Seevaratnam stressed again that the Department of Commerce could not unilaterally effect any changes at this point. However, he stressed that it took 3 years to come to this stage. With the concern over biological warfare at a heightened level, it may not be easy to convince people of relaxing the controls. He said he believed some compromise could be reached. If comments are received, they will be forwarded to the proper committees and working groups.

Dr. R. Murray asked if this means that no exports of such genetically manipulated organisms would be allowed. Mr. Seevaratnam said this was not an embargo, but would require a license to all destinations except Canada. To get a license one must apply through the Bureau of Export Administration, Office of Export Licensing. One, in turn would send such a request to the

Office of Foreign Availability to determine availability abroad. If there is foreign availability, the control must be removed. However, the President holds an overriding veto if the National Security Council is convinced it is not in the best interests of the United States to release it from control. Mr. Seevaratnam said Mr. Ian Baird is the Director of the Office of Export Licensing and gave his phone number as 377-8735.

Dr. McGarrity asked if pathogenicity of the coding sequences, added or deleted, was the overriding issue. Mr. Seevaratnam said this was one issue, but the overriding concern was for biological warfare. Further, not being a microbiologist, he could not answer the question. He did indicate that all applications are sent to U.S. Government laboratories for evaluation, and they determine whether there should be any concern.

Dr. Schaechter asked how long it took to obtain a license. Mr. Seevaratnam replied it used to take 60 days, but due to streamlining now in place it should be turned around in approximately two weeks, provided that the application was properly submitted.

Dr. Riley asked about the list of hazards contained in the proposed document, and how they were so designated. Mr. Seevaratnam said they were compiled by the Centers for Disease Control (CDC) but that the Department of Commerce will review and change those groups to be released on the basis of recommendations from the BIOTAC. He added that it was prepared quickly and technical errors will be corrected.

Dr. Robert McKinney of the National Institutes of Health said this classification of Class 1-4 agents was promulgated in 1974, and it should only be used as a frame of reference. He said some of the changes in classification and biosafety level requirements can be found in the Biosafety Guidelines. With the rapidity of progress in science and technology, he suggested that other approaches be considered rather than setting these requirements as absolutes.

Mr. Seevaratnam said the Department of Commerce is receptive to comments from the Committee as well as any of its members or the scientific community at large and is open to revising the regulations if necessary.

Dr. Greifer of the U.S. Department of Commerce asked if a person in private industry, not receiving Government support, required a license if he handcarries altered microorganisms outside the country to perform experiments outside the U.S. Mr. Seevaratnam said that any tangible commodities leaving the borders of the U.S. constitutes an export and could require licensing. Furthermore, intellectual property could be exported without leaving the country, merely by giving such property to a foreign

national within the United States.

Dr. McGarrity thanked Mr. Seevaratnam and called on Dr. Atlas to lead off discussion on a related agenda item, number IX, "Proposal to Amend Appendix H of the **NIH Guidelines.**"

IX. PROPOSAL TO AMEND APPENDIX H OF THE NIH GUIDELINES (tabs 1361/II and 1372)

Dr. Atlas said the **NIH Guidelines** now state:

> "For purposes of shipping, any organism containing recombinant DNA is to be shipped as an etiologic agent."

He said that does not mean it is an etiologic agent, but merely that it shall be shipped as one.

Dr. Atlas noted the U.S. Postal Service had raised some concern by publishing new rules on shipment of etiologic agents and this had caused some alarm in the scientific community. Therefore, the Subcommittee on Definitions had met and proposed modifications saying that: (1) if the host organism was an etiologic agent that appeared on a series of lists, it would be treated as an etiologic agent, or (2) if the host organism contained any recombinant DNA derived from one of those organisms on the list, it would be treated as an etiologic agent, thus relaxing the **NIH Guidelines** while maintaining safety.

The RAC sent this back to the Subcommittee on Definitions for further refinement. The Subcommittee met on July 12, 1989, and recommended that Appendix H be replaced as follows:

"Appendix H--Shipment.

"Recombinant DNA molecules contained in an organism or in a viral genome shall be shipped under the applicable regulations of the U.S. Postal Service; the U.S. Public Health Service [42 CFR, Part 72; the U.S. Department of Agriculture [9 CFR, subchapters D and E; 7 CFR, Part 340]; and/or the U.S. Department of Transportation [49 CFR, Parts 171-179].

"For purposes of the **NIH Guidelines:**

"Host organisms or viruses will be defined as etiologic agents regardless of whether or not they contain recombinant DNA if they are regulated as human pathogens under U.S. Public Health Service [42 CFR, Part 72] or as animal pathogens or plant pests under the Animal and Plant

Health Inspection Service (APHIS), U.S. Department of

Agriculture [Titles 8 and 7 CFR, respectively].

"Additionally, host organisms and viruses will be defined as etiologic agents if they contain recombinant DNA when:

"A. the recombinant DNA includes the complete genome of a host organism or virus regulated as a human or animal pathogen or a plant pest; or

"B. the recombinant DNA codes for a toxin or other factor directly involved in eliciting human, animal or plant disease or inhibiting plant growth and is carried on an expression vector or within the host chromosome and/or when the host organism contains a conjugation proficient plasmid or a generalized transducing phage; or

"C. the recombinant DNA comes from a host organism or virus regulated as a human or animal pathogen or as a plant pest and has not been adequately characterized to demonstrate that it does not code for a factor involved in eliciting human, animal or plant disease.

"Appendix H-1--Footnotes and References of Appendix H.

"For further information on shipping etiologic agents, please contact: (1) Centers for Disease Control, ATTN: Biohazards Control Office, 1600 Clifton Road, Atlanta, Georgia 30333, (404) 639-3883, FTS 236-3883; (2) Department of Transportation, ATTN: Office of Hazardous Materials Transportation, 400 7th Street, S.W., Washington, D.C. 20590, (202) 366-4545; or (3) Department of Agriculture, ATTN: Animal & Plant Health Inspection Service, 6505 Belcrest Road, Hyattsville, Maryland 20782, (301) 436-7885 for Animal Pathogens, (301) 436-7612 for Plant Pests."

Dr. Atlas said references to lists have been deleted as they are not updated. In fact, HIV has not made its way onto such lists. Therefore, it could provide a loophole for shipping materials that could be potentially hazardous. The Subcommittee felt it better not to rely on CDC and the Animal and Plant Health Inspection Service (APHIS) for producing knowledge of what is needed to have a host organism be considered an etiologic agent. Further, a diagram and reference to a diagram had been deleted as the diagram had not kept up with regulatory changes. A simple Appendix is added for reference which gives the phone numbers to contact in all affected agencies.

Mr. Mannix said two comments had been received, one noting a **Code of Federal Regulations** citation that was not available at the time of the drafting of the proposal, which is 39 CFR, Part 111, which should be incorporated in the first full paragraph after

the words "U.S. Postal Service."

Dr. McVicar said there are three agencies which regulate the shipment of etiologic agents: the Department of Transportation, the U.S. Postal Service (USPS), and the Public Health Service (PHS). He said the PHS has authority to regulate interstate shipments of etiologic agents. The other two agencies regulate shipment of hazardous substances, ranging from chemicals to radioactive materials. He said the PHS authority was promulgated in 1980 and is in the process of being revised and includes a list of etiologic agents similar to the one which was removed from Appendix H which was derived from a 1969 CDC publication entitled *The Classification of Agents on the Basis of Hazard*.

Dr. McVicar said in listening to discussions of product versus process in the morning session, he was drawn back to the issue of agents and hazard classification. He hoped we were moving away from equating genetic manipulation with hazardous. He said there is concern that classification lists have not been kept up to date. He said if such schemes are to be utilized for regulation, there was a need to develop an algorithm for dealing with new agents so they can be properly classified and handled. He said he supported the new revision of Appendix H.

Dr. McGarrity asked if discontinuing to list all agents with recombinant DNA in them as etiologic agents would be accepted by other agencies such as the CDC. Dr. McVicar said he believed this was not a problem in that most agencies did not possess the expertise to be able to make such judgments and many of them already rely on the Public Health Service regulations to govern what they define as etiologic agents.

Dr. Atlas pointed out that recombinant DNA containing agents have never been classified as being etiologic, but merely that they were to be shipped as etiologic agents for safety purposes.

Dr. McKinney added that it would be more helpful to classify agents by the types of packaging and containerization that is required for shipment of each class. He suggested replacing the term "...will be defined as..." with "...will be shipped as...." resulting in the following wording for the paragraph beginning "For purposes of the **NIH Guidelines:**"

> "Host organisms or viruses will be **shipped** as etiologic agents regardless of whether or not they contain recombinant DNA if they are regulated as human pathogens under U.S. Public Health Service [42 CFR, Part 72] or as animal pathogens or plant pests under the Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture [Titles 8 and 7 CFR, respectively]."

Dr. Childress said this wording precisely solved a problem that

concerned the Subcommittee. Dr. Atlas said the same terminology should be substituted in the paragraph beginning, "Additionally, host organisms and viruses will be **shipped**...."

Mr. Mannix suggested deleting the introductory phrase, "For purposes of the **NIH Guidelines**." The purpose relates to USPS regulations rather than the **NIH Guidelines**.

Dr. McKinney said this was a jurisdictional issue. The **NIH Guidelines** are promulgated by the NIH which has no regulatory power. While they have been adopted by some regulatory agencies, the NIH cannot impose them on regulatory agencies. Therefore, he said the phrase "For purposes of the **NIH Guidelines**" should be retained to make clear the frame of reference in the event that these shipping instructions are referred to out of context.

Mr. Mannix suggested revising this to say, "For the purpose of this appendix," because the entire appendix deals with shipment and cites all other pertinent regulations. He asked if the appendix applied to any other section or appendix of the **NIH Guidelines**. Dr. McGarrity said an appendix stands by itself.

Dr. Miller said if the conditions of paragraphs A, B, or C were met he believed the agent would be classified as a pathogen, and therefore fall under regulatory purview. He asked if these were indeed necessary to include in the **NIH Guidelines** as they would already be regulated by other agencies.

Dr. McVicar said it would depend on definitional status. If an etiologic agent were defined as one which was disease provoking, it would probably not fall into the category of agent described in paragraph A. Dr. Miller suggested paragraphs A, B, and C not be included unless someone could present a reason for them to be there.

Dr. McGarrity said his understanding was that the purpose of this revision was twofold: (1) to define etiologic agents as those containing pathogens; and (2) to allow other things, containing recombinant DNA, but not from etiologic agents, to be excluded from the classification and not be shipped as etiologic agents.

Dr. Atlas agreed with this interpretation. He said A, B, and C relate specifically to the purview of the RAC in terms of definition and would allow for free shipment of most materials.

Dr. Miller said it sends an incremental message that if something contains recombinant DNA, it may be rational to over-regulate it.

Dr. John Payne of USDA said the language closely mirrored language used for shipment of plant pests at APHIS. He said their regulations were based on the rationale of what would happen if it was released accidentally in shipment. The concern

would not be whether it contained recombinant DNA but whether it was infectious.

Dr. Gellert asked if the intention in paragraph B was to cover a host containing a conjugation proficient plasmid or a generalized transducing phage, whether or not it contained a gene for a toxin, because of the wording "and above" and "and/or below" in the paragraph.

Dr. Atlas said the intention was to regulate it when it was carrying a gene from a pathogen, and there was reason to think it may be mobilized.

Dr. Gellert also questioned the term "the complete genome" as used in paragraph A. He said a relatively trivial aberration could result in something fairly dangerous being shipped without proper control.

Dr. Atlas said if this were the case, it would contain a gene for a toxin or other factor which would be captured under the criterion of paragraph B. He said paragraph A could be deleted because paragraph B would in fact take care of this type of problem.

Dr. McVicar said everything goes back to whether something being shipped can or cannot cause disease. He said the burden of proof falls on the person who is shipping the molecule to be able to know whether it is infectious or not. If no proof is available, then it is preferable to err on the side of safety. He said the CDC regulation simply comes down to whether it causes or is capable of causing human disease then it is an etiologic agent and will be regulated.

Dr. McKinney said he would favor retaining this as guidance and clarification for people in making shipping decisions. He said it did not impose any new requirements on people for shipment, but rather the opposite was true. The new Appendix H probably will relieve 95 percent of investigators from having to ship recombinant DNA as an etiologic agent.

Dr. Neiman said, in thinking about Dr. Atlas' suggestion of deleting paragraph A, he recalled that in the case of retroviruses, viral DNA may retain its infectiousness and have inactivated genes with regard to pathogenicity. Yet such genes are capable of being repaired in subsequent replication cycles.

Dr. McVicar once again emphasized that even in this case if the viral DNA was not pathogenic, there would be no need for regulation. Dr. Neiman agreed.

Dr. Atlas moved that the RAC adopt this revision of Appendix H to

the **NIH Guidelines** with the following modifications that have been suggested:

1. Insert the parenthetical phrase "39 CFR, Part 111," after the words "U.S. Postal Service," in the first full paragraph;

2. Delete the word "defined" and replace it with the word "shipped" in the first and last paragraphs.

Mr. Mannix seconded the motion. There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 15 in favor, none opposed, and no abstentions.

Dr. McGarrity called on Dr. Schaechter to open the discussion of the next agenda item, "Proposed Amendment to the **NIH Guidelines** Regarding *Klebsiella oxytoca*.

X. **PROPOSED AMENDMENT OF NIH GUIDELINES REGARDING KLEBSIELLA OXYTOCA**: (tabs 1361/IV and 1368)

Dr. Schaechter said *Klebsiella oxytoca* is an environmental gram-negative member of the family *Aerobacteriacae*, previously named *Klebsiella pneumoniae* and *Aerobacter aerogenes*, which exhibits low level toxigenicity for humans and animals and unknown toxigenicity for plants. He said it had been implicated in occasional opportunistic infections in debilitated or immunocompromised patients.

Dr. Schaechter said the proposal from Biotechnica was to modify the perceived level of containment for the strain M5a1 which has been used in nitrogen fixation research in the laboratory for over 30 years. He said it has been grown on a pilot plant scale with no untoward effects. When injected into rabbits for the purpose of making antibodies, it showed no pathogenic properties.

The strain has been considered for exemption by several European regulatory agencies and has lately been exempted by the Genetic Manipulation Advisory Group, the British regulatory agency. Dr. Schaechter said approval of the proposed amendment to the **NIH Guidelines** regarding *Klebsiella oxytoca* should be granted.

Dr. B. Murray said she agreed with everything Dr. Schaechter had presented. Dr. Clewell said he agreed with Dr. Schaechter, but noted only the proposal for cloning under Biosafety Level 1 conditions was something new. He agreed it was a reasonable request.

Dr. Schaechter moved the approval of this request. Dr. Gellert seconded the motion. Dr. McGarrity asked for further discussion, and hearing none, called for a vote on the motion. The motion

carried by a vote of 14 in favor, none opposed, and one abstention.

Dr. McGarrity said the next item on the agenda, "Proposal to Update the Classification of Oncogenic Viruses in Appendix B-II of the **NIH Guidelines**," was based on a letter from Dr. McKinney, did not appear in the **Federal Register**, and as such no final action could take place. He called on Dr. McKinney to present the proposal.

XI. **PROPOSAL TO UPDATE THE CLASSIFICATION OF ONCOGENIC VIRUSES IN APPENDIX B-II OF THE NIH GUIDELINES** (tab 1371)

Dr. McKinney said his office continues to receive calls for guidance on viruses, particularly with recent interest in retroviruses and amphotrophic viruses. The classification was published in 1974 and is deficient in the following:

1. It fails to list a variety of agents;

2. There are probably a number of viruses in the category of "Moderate Risk" that could be classified as "Low Risk" and thus used at a lower containment level; and

3. The classification of Low, Moderate and High risk is inconsistent with current terminology, particularly with the **NIH Guidelines** which now use the biosafety levels.

Dr. McKinney said he wrote to ORDA to encourage action by the RAC, realizing it is not a simple task, but one which is urgently needed by the scientific community.

Dr. McGarrity noted that the letter was received too late for incorporation into the **Federal Register** notification for this meeting and said it would automatically be submitted for publication before the next RAC meeting.

Dr. McKinney said he did not feel the letter needed to go in the **Federal Register** and delay action by the RAC until its next meeting. Rather the product of any action taken by the RAC would be published for comment since that would represent a change to the **NIH Guidelines**.

Dr. McGarrity said he did not intend to cut off debate, but merely wanted to clarify the status of the proposal and what actions were within the purview of the RAC at this time.

Dr. Neiman said he did not understand what this proposal had to do with the RAC. He said the CDC or other organizations were responsible for classification of potential or real human viral

pathogens. Dr. McKinney said the reason he brought the proposal before the RAC is that such a classification is published and retained only in the **NIH Guidelines**. He said this classification originally came from an NCI document which is out of print and no longer available. He said he did not expect RAC to actually determine these classifications and update them, but merely to provide the mechanism through which this could be facilitated.

Dr. McGarrity asked if the NCI was currently doing anything or was proposing doing anything in this area. Dr. McKinney said they were not currently doing anything and reiterated that the NCI document would not be reprinted.

Dr. McVicar said the same applied to the classification of other microorganisms which appears only in the **NIH Guidelines**. He said when he is queried by investigators, he refers them to the **NIH Guidelines** since this is the only place such a classification is printed on a regular basis, although there is no update.

Dr. Neiman said he did not believe the RAC to have the proper expertise or mechanism to take on reclassifying all the retroviruses in existence and suggested the RAC request appropriate agencies to update these lists. Dr. R. Murray concurred with Dr. Neiman that such responsibility was not within the framework of the RAC. Dr. Riley agreed and added that the RAC should encourage responsible agencies to bring these lists up to date.

Dr. McKinney said he hoped the RAC could serve as a focal point and sponsor for convening a committee that could review these classification lists. Dr. McGarrity asked for specific wording for such a proposal and a suggestion as to who should be the recipient of any such request. Dr. Neiman said, since the RAC was advisory to the Director of NIH, any such request should go to him.

Dr. John McVicar of the CDC said, in light of the fact that substantial portions of the **NIH Guidelines** are subject to external review processes, it may be of benefit to establish a subcommittee of the RAC to ensure such lists are kept current.

Dr. R. Murray said he felt this was more an administrative matter than a policy matter. If this situation were brought to the attention of the agencies who originally promulgated these lists, those agencies could update them. He agreed that an update is necessary but was unsure the RAC could facilitate it.

Dr. R. Murray made the following motion:

> "That this Committee communicate with the Office of the Director of NIH, advising him of our being made aware of this deficiency and that these lists be updated or revised

in accordance to new information."

Dr. Neiman seconded the motion. Dr. Vidaver said the USDA should be brought into the process so a consolidated list of human and animal pathogens and plant pests can be dealt with.

Dr. R. Murray agreed to append the following phrase to the last sentence of the motion:

> "...and that the NIH Director convey these concerns to other appropriate authorities."

There being no further discussion on the motion, it was put to a vote and passed unanimously by a vote of 14 in favor, none opposed, and no abstentions.

XII. FUTURE MEETING DATES (tab 1370)

Dr. McGarrity called attention to a new date for the October 1990 meeting and two new dates in 1991. He noted the next meeting of the Human Gene Therapy Subcommittee is scheduled for December 4, 1989.

XIII. ADJOURNMENT

Dr. McGarrity personally thanked Dr. Neiman, Dr. Roberts, and Mr. McCreery, and other members retiring from the Committee and said it had been a pleasure and honor to work with them.

Having concluded the agenda, and there being no further business to be discussed, Dr. McGarrity adjourned the Committee at 2:50 p.m., on October 6, 1989.

Nelson A. Wivel, M.D.
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date: 2/20/90

Gerard J. McGarrity, Ph.D.
Chair
Recombinant DNA Advisory Committee
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October 1989

DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 7, 1989

To: Members
Recombinant DNA Advisory Committee

From: Director
Office of Recombinant DNA Advisory Committee

Subject: October 6, 1989, Meeting - Mailing I

The next meeting of the committee will be on October 6, 1989, at the National Institutes of Health, Building 31C, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892. This will be a one day meeting that will begin at 9 a.m. Please note that we have a very full agenda and make your plans accordingly. **It is unlikely that the meeting will adjourn before 5 p.m.**

Room reservations have been made for the evening of October 5, 1989, at the Marriott Hotel in Bethesda (301-897-9400) for those who requested accommodations. If you wish to change or cancel these reservations, please contact Ms. Becky Lawson in my office at 301-496-9838. For arrival after 6 p.m., a deposit in the amount of one night's stay is required by either a check in the amount of $76 or a major credit card authorization. **The hotel will not hold the room past 6 p.m. without a deposit.**

A tentative agenda and list of primary reviewers are included in this mailing. Drs. Walters, Vidaver, and McVicar will attend the meeting as **ad hoc** consultants. Dr. Lazen and Mr. Seevaratnam will be making presentations to the committee.

Enclosed for your consideration at the October 6, 1989, meeting are the following items:

Please bring these materials with you to the meeting.

Nelson A. Wivel

Nelson A. Wivel, M.D.

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

BUILDING 31C, CONFERENCE ROOM 6
BETHESDA, MARYLAND

OCTOBER 6, 1989

TENTATIVE AGENDA[1]

I.	Call to Order		Dr. McGarrity	9:00 a.m.
II.	Minutes of January 30, 1989, Meeting	#1362	Dr. B. Murray Mr. Carner Mr. McCreery	9:15 a.m.
III.	Amendment to Recombinant DNA Advisory Committee Charter	#1363	Dr. McGarrity	9:30 a.m.
IV.	Presentation from the National Research Council's Study entitled: *Scientific Evaluation of the Introduction of Genetically Modified Microorganisms and Plants into the Environment*	#1361/V 1369	Dr. McGarrity Dr. Lazen Dr. Mulligan Dr. Riley	9:45 a.m.
	Coffee Break			10:15 a.m.
V.	Amendment of Section I-B of the NIH Guidelines	#1361/I 1364 1365	Dr. Riley Dr. Vidaver Dr. Bourquin Dr. Roberts Mr. Bedell	10:30 a.m.

[1]All times on this agenda are estimates. The actual time for consideration of an item may be earlier or later than indicated.

VI.	Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into Human Subjects	#1361/II 1366 1367	Dr. Walters. Dr. Childress Dr. McIvor Dr. Erickson Dr. Acosta Dr. R. Murray Dr. Neiman	11:15 a.m.
	Lunch			12:15 a.m.
VII.	Presentation from the Department of Commerce on an Interim Rule regarding the export of microorganisms	#1361/V.	Mr. Seevaratnam	1:30 p.m.
VIII.	Proposal to Amend Appendix H of the NIH Guidelines	#1361/III	Mr. Brewer. Dr. Atlas Mr. Mannix Dr. Musgrave Dr. McVicar	2:00 p.m.
	Coffee Break			3:00 p.m.
IX.	Proposed Amendment of NIH Guidelines regarding *Klebsiella oxytoca*	#1361/IV 1368	Dr. Schaechter Dr. B. Murray Dr. Clewell Dr. Gellert	3:15 p.m.
X.	Future Meeting Dates	#1370	Dr. McGarrity.	4:15 p.m.
XI.	Adjournment		Dr. McGarrity.	4:30 p.m.

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